REMARKS

I. Status of the claims

Claims 44-74 are pending. Claims 57-69 and 71-74 remain withdrawn and claims 1-41 remain cancelled. No claims have been amended in this response.

II. Priority

The examiner has requested Applicants to identify where in the priority documents SEQ ID Nos. 27-30 may be found. PCT application PCT/US2004/018848, filed June 14, 2004, lists SEQ ID Nos. 27-30 in Table 3. See page 15. Claims 2 and 20 of the PCT application also list these sequences.

III. Rejections under 35 U.S.C. § 112, second paragraph

The examiner has rejected claims 44-56, and 70 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. The examiner states that because the claims recite "the terminal base pair of the first double-stranded end" and "the terminal base pair of the second double-stranded end," it is unclear to which termini the claims are referring.

Applicants respectfully disagree. The claims clearly state that there are two double stranded ends, recited as "first and second double-stranded ends." The term "terminal base pair" is defined in the specification at page 9. The specification states that the term "terminal base pair" refers to the last nucleotide base pair on one end of the duplex region of the dsRNA. See page 9, lines 26-27. The specification further states that "[w]here a dsRNA has a nucleotide overhang at one or both ends of the duplex structure, the last nucleotide base pair(s) immediately adjacent the nucleotide overhang(s) is the terminal base pairs at that end(s) of the dsRNA." See page 9, lines 29-31. Based on this disclosure, one skilled in the art would clearly recognize that terms "the terminal base pair of the first double-stranded end" and "the terminal base pair of the second double-stranded end" are referring to the last nucleotide base pair at the first and the second double-stranded ends.

In view of the supporting specification, there is nothing unclear in the use of these claim terms. Accordingly, Applicants respectfully request that the examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

IV. Rejections under 35 U.S.C. § 112, first paragraph

The examiner has rejected claims 44-56, and 70 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the specification does not adequately describe a representative number of species. One skilled in the art, according to the examiner, would therefore reasonably conclude that adequate written description is lacking for the genus of inhibitory compounds claimed by Applicants.

Applicants respectfully traverse this rejection. According to MPEP § 2163.04, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See In re Marzochhi*, 439 F.2d 220, 224 (CCPA 1971). The examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). In this case, the examiner has not presented sufficient evidence or reasoning to rebut the presumption that written description is adequate.

Instead, the examiner points to select passages in the specification and concludes that the "disclosure fails to provide a representative number of species." See page 6 of the Office Action. A claimed genus, however, can be adequately described by disclosing either a representative number of species in that genus or its relevant identifying characteristics, such as complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *See Enzo Biochem, Inc. v. GenProbe Inc.*, 323 F.3d 956, 964 (Fed Cir. 2003).

The examples and supporting specification, which describes the functional characteristics of the claimed invention, satisfies the written description requirement. Prior to this invention, means for stabilizing dsRNA against degradation were insufficiently known. In this invention, however, Applicants have demonstrated that dsRNA having specific placement of GC base pairs

at the double stranded terminal ends and specific sequences, e.g. 5'-GC-3', for the single-stranded overhangs show unexpected improvement in both serum stability and thermal stability. This is exemplified in Examples 5 and 6.

In Example 5, three different dsRNA molecules (BCL20, B133, and P3) were studied, each having GC base pairs in different locations. In dsRNA BCL20, each terminal base pair is a GC base pair, at least two out of the first four nucleotides are GC base pairs at each double stranded end, and a 5'-GC-3' single stranded overhang is present at the 3'-end of antisense strand. This dsRNA was negligibly degraded in the serum. In dsRNA B133, at least two out of the first four nucleotides are GC base pairs at each double stranded end, and a 5'-GC-3' single stranded overhang is present at the 3'-end of antisense strand. This dsRNA was degraded at a slightly higher rate than BCL20. In dsRNA P3, only one terminal base pair is GC base pair, and a 5'-GC-3' single stranded overhang is present at the 3'-end of antisense strand. This dsRNA was degraded almost immediately in serum.

Based on the three different dsRNA molecules having different placement of the GC base pairs, Example 5 demonstrates that specific placement of GC base pairs in the dsRNA results in dsRNA serum stability. Placement of the GC base pairs set forth in the manner recited in Applicant's claimed invention thus demonstrates an improved capacity of the dsRNA to mediate RNA interference.

In Example 6, dsRNA P4 has a single-stranded 5'-GC-3' overhang on the antisense strand and a GC base pair on the double-stranded end, and dsRNA P2 has a single-stranded 5'-UU-3' overhang on the antisense strand and no terminal GC base pair at the double-stranded end. When tested for melting temperature (Tm), dsRNA P4 showed a higher melting temperature than dsRNA P2 (69.6 ^{o}C vs. 67 ^{o}C). As discussed in the specification, this increased thermodynamic stability of the dsRNA translates into higher resistance to exonucleolytic degradation. See page 89, lines 7-10. Thus, Example 6 demonstrates that specific placement of the GC base pair results in increased thermodynamic stability of the dsRNA.

It is the specific placement of the GC base pairs that Applicants are claiming in this invention. Based on the above examples illustrating the improved properties resulting from this particular placement, one skilled in the art would clearly recognize that Applicants have possession of the invention. Certainly, the examiner has not demonstrated by preponderance of

the evidence why one skilled in the art would *not* be in possession of the claimed invention. Accordingly, Applicants respectfully request the withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

V. Rejections under 35 U.S.C. § 103

The examiner has rejected claims 44-56 and 70 under 35 U.S.C. § 103 as being unpatentable over PCT Application Publication No WO2004/44321 to Tuschl et al ("Tuschl") in view of U.S. Patent No 7,345,027 to Tolentino et al. ("Tolentino").

The examiner states that Tuschl teaches RNAi molecules consisting of first and second single RNA strands, the first strand being antisense to a target gene and 19-28 bases in length, and at least one single-stranded overhang that is 2-4 nucleotides in length. Tuschl is further stated to teach routine experimental approaches to systematically compare the stability and target gene inhibiting capacity of RNAi molecules. Tolentino, according to the examiner, teaches RNAi molecules with 3' overhangs on one or both strands between 1-6 bases, the importance of location of purines and modified residues on the RNAi strands, and the enhanced stability, target binding, and inhibition of expression of the RNAi molecules. Tolentino is also stated to teach the design, testing and optimization of RNAi molecules in their ability to inhibit target gene expression. Based on these alleged teachings, the examiner concludes that one would have been motivated to alter the bases and insert purines at positions within the RNAi as instantly claimed.

Applicants respectfully traverse this rejection. The claimed invention relates to a double stranded ribonucleic acid, where each terminal end of the double-stranded RNA comprises either a terminal GC base pair or at least two GC base pairs in the first four base pairs and the dsRNA inhibits the expression of said target gene by means of RNA interference. As emphasized above, each terminal end either terminates with a GC base pair or there are at least two GC base pairs in the first four base pairs from the end. Tuschl and Tolentino, either alone or in combination, fail to teach or suggest this feature.

While the examiner relies on Tuschl for disclosing RNAi molecules comprising 3'end overhangs, a complete reading of Tuschl would not lead one skilled in the art to use a 5'-GC-3' overhang at the 3'end of the antisense strand. Tuschl teaches the use of a **UG**, **UU**, **TdG** or **TT** overhang at the 3'end of the antisense strand, stating that "[t]he most efficient siRNA duplexes

that reduced target expression more than 10-fold, were of the sequence type NN/**UG**, NN/**UU**, NN/**TdG**, and NN/**TT** (N, any nucleotide)." See page 48, lines 10-12.

Furthermore, while Tolentino suggests inclusion of purines in the single stranded overhangs, one skilled in the art would not have, based on this teaching, been motivated to place a purine directly adjacent to the terminal base pair of the double-stranded RNA. Tuschl discloses that siRNAs with antisense strands having **AA** and **GG** as 3'end overhangs were less effective in RNA interference. Both these overhangs have a purine (A or G) that is directly adjacent to the terminal base pair. siRNAs with overhangs comprised fully of purines were less active by a factor of 2 to 4. See page 48, lines 13-15. As discussed above, Tuschl teaches that antisense strands with 3'end overhangs of **UG**, **UU**, **TdG** or **TT** are more effective. In all these more efficacious overhangs, a pyrimidine (U or T) is directly adjacent to the terminal base pair. Based on the complete teachings of Tolentino and Tuschl, one skilled in the art would not be motivated to utilize a dsRNA having a 5'-GC-3' single strand overhang.

The improved properties of the claimed dsRNA are illustrated in Examples 5 and 6. In Example 5, Applicants have found significant advantages associated with having either a terminal GC base pair or at least two GC base pairs in the first four base pairs at each terminal of dsRNA. As shown in Example 5, and discussed *supra*, dsRNAs having a GC base pair and at least two GC base pairs out of the first four nucleotides at each terminal end (dsRNA B133) or dsRNA having at least two out of the first four nucleotides are GC base pairs at each terminal end (dsRNA BCL20) showed enhanced serum stability when compared to dsRNA having a GC base pair at only one terminal end. In Example 6, Applicants have found significant advantages associated with using a 5'-GC-3'- overhang at the 3'-end of the antisense strand. As shown in Example 6, discussed in detail *supra*, the incorporation of a 5'-GC-3'- overhang into a substantially identical dsRNA was shown to lead to an increase in the dsRNA melting temperature (T_m) of 2.6 ^{o}C. The increase in T_m demonstrated in Example 6 and the increased serum stability demonstrated in Example 5 translate to higher dsRNA stability, and therefore an improved capacity of the dsRNA to mediate RNA interference.

Therefore, while both Tuschl and Tolentino teach overhangs on the 3'end, each fails to disclose a double-stranded RNA where each terminal end of the dsRNA contains either a terminal GC base pair or two GC base pairs in the first four base pairs. Certainly, Tuschl and

Tolentino do not suggest the improved properties relating to these claimed features demonstrated by Applicants in the examples. Accordingly, the claimed invention is patentable over the combined teachings of Tuschl and Tolentino, and Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

VI. Conclusion

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

/Jeffrey N. Townes, Reg. No. 47,142/
Jeffrey N. Townes
Registration No. 47,142

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Customer No. 84717
NIXON PEABODY LLP
Suite 900, 401 9th Street, N.W.
Washington, D.C. 20004-2128
202.585.8000